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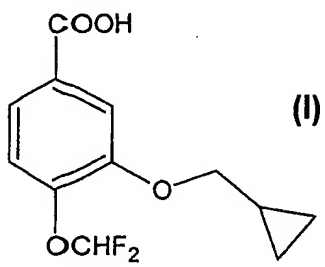
(54) Title: PROCESS FOR THE PREPARATION OF ROFLUMILAST



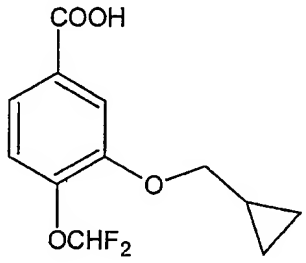
(I)

(57) Abstract: The present invention relates to a process for the preparation of 3-cyclopropylmethoxy-4-difluromethoxy benzoic acid of structural Formula I, and to the use of this compound as an intermediate for the preparation of roflumilast.

PROCESS FOR THE PREPARATION OF ROFLUMILAST

Field of the Invention

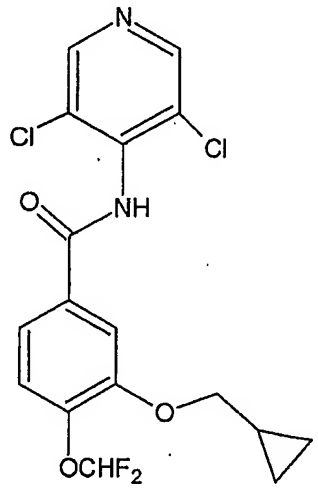
The field of the invention relates to a process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid of Formula I, and to the use of this compound as an intermediate for the preparation of roflumilast.



FORMULA I

Background of the Invention

Chemically, roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)benzamide of Formula VI, and is known from U.S. Patent No. 5,712,298.



FORMULA VI

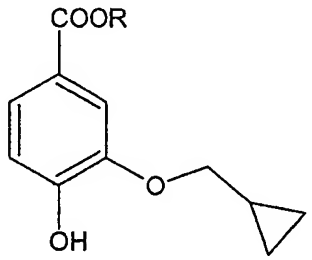
Roflumilast is an effective phosphodiesterase-4-inhibitor (PDE4-inhibitor), which can be used in the treatment of asthma, inflammation, bronchitis, allergy, osteoporosis, dermatoses and disorders related to immune system, heart and kidney.

U.S. Patent No. 5,712,298 discloses the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid comprising reacting 4-hydroxy-3-cyclopropylmethoxybenzaldehyde with dichlorofluoromethane followed by oxidation.

U.S. Patent No. 6,712,274 discloses the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid comprising reacting dihydroxybenzaldehyde with tertiarybutyl difluorochloroacetate in the presence of lithium carbonate and reacting the obtained 4-difluoromethoxy-3-hydroxy benzaldehyde with cyclopropylmethyl bromide in the presence of potassium carbonate followed by oxidation to yield 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid.

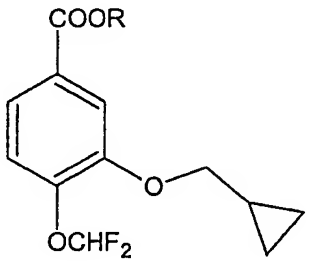
Summary of the Invention

In one general aspect there is provided a process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid. The process includes reacting the compound of Formula II,



FORMULA II

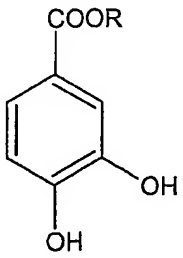
wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, with difluoro methylating agent in the presence of a base to obtain compound of Formula III,



FORMULA III

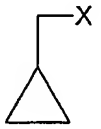
wherein R is as defined above; and desterification of the compound of Formula III to obtain the compound of Formula I.

In another general aspect there is provided a process for the preparation of 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II. The process includes reacting 3,4-dihydroxy benzoate of Formula IV,



FORMULA IV

wherein R is as defined above, with cyclopropylmethyl derivative of Formula V,



FORMULA V

wherein X is a leaving group, in the presence of a base.

In another general aspect there is provided a novel compound, 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II.

In another general aspect there is provided a novel compound of Formula III.

In another general aspect there is provided a process for the preparation of roflumilast. The process includes reacting compound of Formula I with 4-amino-3,5-dichloro pyridine.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of roflumilast; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have developed an efficient process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid. The process involves reacting the

compound of Formula II, wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, with difluoro methylating agent in the presence of a base to obtain compound of Formula III, wherein R is as defined above; and desterification of the compound of Formula III to obtain the compound of Formula I.

Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, secondary butyl and tert- butyl groups. Examples of alkenyl groups include vinyl, allyl, isopropenyl, pentenyl and hexenyl groups. The substituted phenyl includes phenyl substituted by 1-3 substituents, which are independently bromine, chlorine, fluorine, C_1-C_4 alkyl, C_1-C_4 alkoxy, and nitro groups. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy and butoxy groups. The substituted benzyl includes p-nitro benzyl, p-methoxy benzyl, o-nitro benzyl, p-bromo benzyl, and 2,4,6-trimethyl benzyl groups.

The difluoro methylating agent which can be used for preparing 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid of Formula I include difluorochloromethane (Freon-22®), alkyl difluorochloroacetate such as methyl difluorochloroacetate, ethyl difluorochloro acetate and tertiarybutyl difluorochloroacetate.

The bases which can be used include organic and inorganic bases. Examples of organic bases include trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5-diazabicyclo-[4.3.0]-non-5-ene), 4-dimethylamino pyridine and mixtures thereof. Examples of inorganic bases include alkali metal carbonate, bicarbonate, hydroxide and mixtures thereof. Examples of alkali metal carbonates include lithium carbonate, sodium carbonate and potassium carbonate. Examples of alkali metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of alkali metal hydroxides include sodium hydroxide and potassium hydroxide.

The reaction of compound of Formula II with difluoromethylating agent may be carried out in the presence of phase transfer catalyst. Examples of such phase transfer catalysts include quaternary ammonium salts such as tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2-butylammonium chloride, trimethylcyclopropylammonium

chloride, tetrabutylammonium bromide and t-butylethyldimethylammonium bromide; quaternary phosphonium salts such as tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, and tetraphenyl phosphonium chloride.

The reaction of compound of Formula II with difluoromethylating agent may be carried out in the presence of a suitable solvent. Suitable solvents are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include alkyl ethers such as diethylether, diisopropylether and dimethoxyethane; nitriles such as acetonitrile and benzonitrile; alcohols such as methanol, ethanol, isopropanol and butanol; ketones such as acetone and methyl isobutyl ketone; chlorinated hydrocarbons such as methylene chloride, ethylene dichloride and carbon tetrachloride; esters such as ethylacetate and isopropylacetate; hydrocarbons such as benzene, xylene, toluene , hexane, cyclohexane, heptane and octane; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; cyclic ethers such as dioxane and tetrahydrofuran, and mixtures thereof.

The reaction may be carried out at a temperature of from about 20°C to about 120°C, for example at a temperature of from about 25°C to about 50°C.

The compound of Formula III is converted to the compound of Formula I by conventional methods including hydrolysis or hydrogenation, in case R is a benzylic group.

Examples of leaving group X, in the compound of Formula V, include chlorine, bromine, iodine, sulphate and tosylate.

The base, phase transfer catalyst and solvent, which may be used for preparing 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II from compound of Formula IV, can be the same as those which can be used in reaction of compound of Formula II with difluoromethylating agent.

The reaction may be performed at a temperature from about 20°C to about 120°C. In particular, it may be performed at a temperature from about 25°C to 50°C.

In general, roflumilast of Formula VI is prepared by reacting an activated derivative of the acid of Formula I, such as acid halide or a reactive ester, with 4-amino-3,5-dichloro pyridine. For example, roflumilast can be prepared by reacting the

corresponding acid chloride of the compound of Formula I with 4-amino-3,5-dichloro pyridine in the presence of sodium hydride in tetrahydrofuran.

The resulting roflumilast may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The compositions include dosage forms suitable for oral, buccal, rectal, and parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The oral dosage forms may include solid dosage forms, like powder, tablets, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions, emulsions, pastes and elixirs. Parenteral dosage forms may include intravenous infusions, sterile solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be reconstituted with sterile water for parenteral administration, and the like.

The roflumilast can be administered for the treatment the treatment of asthma, inflammation, bronchitis, allergy, osteoporosis, dermatoses and disorders related to immune system, heart and kidney in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

In the following section embodiments are described by way of examples to illustrate the process of invention. However, these do not limit the scope of the present invention. Variants of these examples would be evident to persons ordinarily skilled in the art.

Example 1: Preparation of 3-Cyclopropylmethoxy-4-hydroxy methyl benzoate

3,4-Dihydroxy methyl benzoate (50 g) was stirred with cyclopropylmethyl bromide (50.2 g) and potassium carbonate (82.1 g) in acetone (350 ml) for 18 hours at 40°C. The reaction mixture was filtered over a hyflo bed followed by concentration of the organic layer.

The crude product was purified over a silica gel column (eluting with 5 % ethyl acetate in hexane) to obtain the title product.

Yield: 16 g.

HPLC Purity: 99.5%

Example 2: Preparation of 3-Cyclopropylmethoxy-4-difluoromethoxy benzoic acid

The product obtained from Example 1 (10 g) was subjected to difluoromethylation using difluorochloromethane, 35 % w/w sodium hydroxide aqueous solution (50 ml), tetrabutyl ammonium bromide (5.9 g) in toluene (100 ml) as solvent at 20 to 35° C. The resulting product, 3-cyclopropylmethoxy-4-difluoromethoxy methyl benzoate was hydrolyzed *in situ* by adding 50 ml water and heating the reaction mixture to 50 to 55°C. pH of the reaction mixture was adjusted to 3-4 by adding concentrated hydrochloric acid at 20 to 30°C followed by extraction with ethyl acetate (48 ml) .The solvent was evaporated under vacuum and the product was collected.

Yield: 10 g.

HPLC Purity: 94.0%

Example 3: Preparation of roflumilast

The product obtained from Example 2 (10g) was heated with thionyl chloride (5.8g) and catalytic amount of dimethylformamide (0.5ml) at 80 to 85°C for 1 hour. The solution was evaporated *in vacuo* and the oily residue was dissolved in dry tetrahydrofuran (50 ml). This was added dropwise at 0°C to a suspension prepared from sodium hydride (3.75 g, 60% suspension) and 4-amino-3,5-dichloro pyridine (9.5g) in dry tetrahydrofuran (50 ml) with stirring. The reaction mixture was stirred for 30 minutes and then acidified to pH 2 with hydrochloric acid (1 N). The reaction mixture was extracted with ethyl acetate. The extracted solvent was washed with sodium bicarbonate solution (5%) and water followed by evaporation in vacuum. The residue was dissolved in methanol (45 ml) at 60°C and 5 ml of water was added to get precipitate. The mixture was then cooled to 10°C and filtered to obtain roflumilast.

Yield: 9.2 g

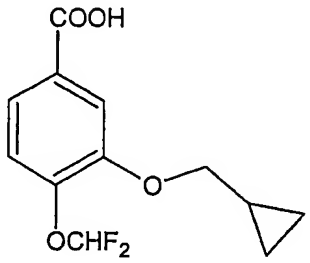
Purity: 99%

m.p.: 157-158°C

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

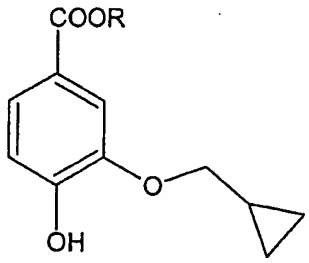
We claim:

1. A process for the preparation of 3-cyclopropylmethoxy-4-difluoromethoxy benzoic acid of Formula I,



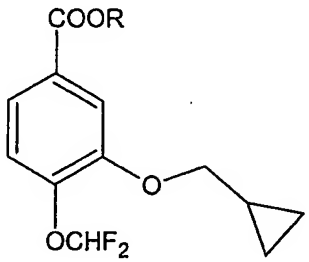
FORMULA I

the process comprising reacting compound of Formula II,



FORMULA II

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, with difluoro methylating agent in the presence of a base to obtain compound of Formula III,



FORMULA III

wherein R is as defined above; and desterification of the compound of Formula III to obtain the compound of Formula I.

2. The process of claim 1, wherein R represents methyl or ethyl.

3. The process of claim 1, wherein the difluoromethylating agent comprises one or more of difluorochloromethane (Freon-22®) and alkyl difluorochloroacetate.

4. The process of claim 3, wherein the alkyl difluorochloroacetate comprises one or more of methyl difluorochloroacetate, ethyl difluorochloroacetate and tertiary butyl difluorochloroacetate.

5. The process of claim 1, wherein the base comprises one or more of inorganic and organic bases.

6. The process of claim 5, wherein the organic base comprises one or more of trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5- diazabicyclo-[4.3.0]-non-5-ene), and 4-dimethylamino pyridine.

7. The process of claim 5, wherein the inorganic base comprises one or more of alkali metal carbonates, alkali metal bicarbonates and alkali metal hydroxides.

8. The process of claim 7, wherein the alkali metal carbonate comprises one or more of lithium carbonate, sodium carbonate and potassium carbonate.

9. The process of claim 7, wherein the alkali metal bicarbonate comprises one or both of sodium bicarbonate and potassium bicarbonate.

10. The process of claim 7, wherein the alkali metal hydroxide comprises one or both of sodium hydroxide and potassium hydroxide.

11. The process of claim 1, wherein the reaction is carried out in the presence of a phase transfer catalyst.

12. The process of claim 11, wherein the phase transfer catalyst comprises one or more of quaternary ammonium salts and quaternary phosphonium salts.

13. The process of claim 12, wherein the quaternary ammonium salt comprises one or more of tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2-butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide, and t-butylethyldimethylammonium bromide.

14. The process of claim 12, wherein the quaternary phosphonium salt comprises one or more of tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, and tetraphenyl phosphonium chloride.

15. The process of claim 1, wherein the reaction is carried out in a solvent.

16. The process of claim 15, wherein the solvent comprises one or more of alkyl ethers, alcohols, ketones, chlorinated hydrocarbons, esters, hydrocarbons, dipolar aprotic solvents, cyclic ethers, and nitriles.

17. The process of claim 16, wherein the ether comprises one or more of diethylether, diisopropylether and dimethoxyethane.

18. The process of claim 16, wherein the alcohol comprises one or more of methanol, ethanol, isopropanol and butanol.

19. The process of claim 16, wherein the ketone comprises one or both of acetone and methyl isobutyl ketone.

20. The process of claim 16, wherein the chlorinated hydrocarbon comprises one or more of methylene chloride, ethylene dichloride and carbon tetrachloride.

21. The process of claim 16, wherein the ester comprises one or both of ethylacetate and isopropylacetate.

22. The process of claim 16, wherein the hydrocarbon comprises one or more of benzene, xylene, toluene, hexane, cyclohexane, heptane and octane.

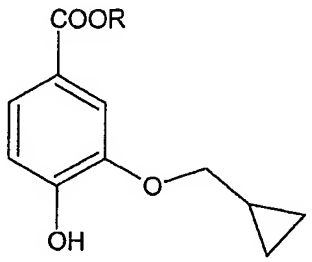
23. The process of claim 16, wherein the dipolar aprotic solvent comprises one or both of dimethylsulfoxide, and dimethylformamide.

24. The process of claim 16, wherein the cyclic ether comprises one or both of dioxane, and tetrahydrofuran.

25. The process of claim 16, wherein the nitrile comprises one or both of acetonitrile and benzonitrile.

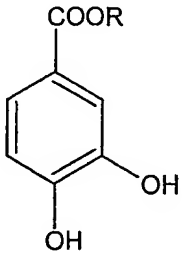
26. The process of claim 1, wherein the reaction of compound of Formula II with difluoro methylating agent is carried out at temperature of from about 25°C to about 50°C.

27. A process for the preparation of 3-cyclopropylmethoxy-4-hydroxy benzoate of Formula II,



FORMULA II

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl, the process comprising reacting 3,4-dihydroxy benzoate of Formula IV,



FORMULA IV

wherein R is as defined above with cyclopropylmethyl derivative of Formula V,

FORMULA V

wherein X is a leaving group, in the presence of a base.

28. The process of claim 27, wherein R represents methyl or ethyl.

29. The process of claim 27, wherein the base comprises one or more of inorganic and organic bases.

30. The process of claim 29, wherein the organic base comprises one or more of trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, DBU (1,8-diazabicyclo- [5.4.0]-undec-7-ene), DBN (1,5- diazabicyclo-[4.3.0]-non-5-ene), and 4-dimethylamino pyridine.

31. The process of claim 29, wherein the inorganic base comprises one or more of alkali metal carbonates, alkali metal bicarbonates and alkali metal hydroxides.

32. The process of claim 31, wherein the alkali metal carbonate comprises one or more of lithium carbonate, sodium carbonate and potassium carbonate.

33. The process of claim 31, wherein the alkali metal bicarbonate comprises one or both of sodium bicarbonate and potassium bicarbonate.

34. The process of claim 31, wherein the alkali metal hydroxide comprises one or both of sodium hydroxide and potassium hydroxide.

35. The process of claim 27, wherein the reaction is carried out in the presence of a phase transfer catalyst.

36. The process of claim 35, wherein the phase transfer catalyst comprises one or more of quaternary ammonium salts and quaternary phosphonium salts.

37. The process of claim 36, wherein the quaternary ammonium salt comprises one or more of tetramethyl ammonium iodide, tetrabutyl ammonium iodide, benzyltributyl ammonium bromide, 1-methylpyridinium iodide, tetramethyl-2- butylammonium chloride, trimethylcyclopropylammonium chloride, tetrabutylammonium bromide, and t-butylethyldimethylammonium bromide.

38. The process of claim 36, wherein the quaternary phosphonium salt comprises one or more of tributylmethylphosphonium iodide, triethylmethylphosphonium iodide, methyltriphenoxyphosphonium iodide, tetrabutyl phosphonium bromide, benzyltriphenyl phosphonium bromide, and tetraphenyl phosphonium chloride.

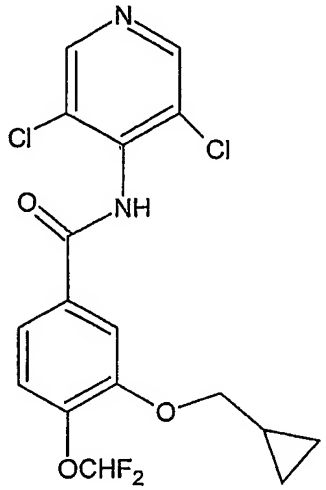
39. The process of claim 27, wherein the reaction is carried out in a solvent.

40. The process of claim 39, wherein the solvent comprises one or more of alkyl ethers, alcohols, ketones, chlorinated hydrocarbons, esters, hydrocarbons, dipolar aprotic solvents, cyclic ethers, and nitriles.

41. The process of claim 27, wherein the leaving group X in the compound of Formula V represents chlorine, bromine, iodine, sulphate and tosylate.

42. The process of claim 27, wherein the reaction of compound of Formula IV with cyclopropylmethyl derivative of Formula V is carried out at temperature of from about 25°C to about 50°C.

43. The process of claim 1, further comprising reacting an activated derivative of the compound of Formula I with 4-amino-3,5-dichloro pyridine,



FORMULA VI

to give a compound of Formula VI.

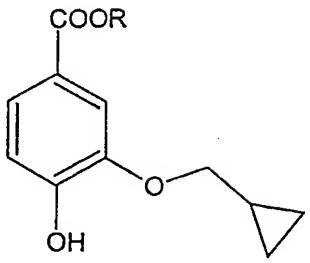
44. The process of claim 43, wherein the activated derivative is acid halide or a reactive ester of the compound of Formula I.

45. The process of claim 44, wherein the reaction of activated derivative of the Formula I with 4-amino-3,5-dichloro pyridine in carried out in the presence of sodium hydride in tetrahydrofuran.

46. A pharmaceutical composition comprising a therapeutically effective amount of roflumilast obtained by the process of claim 43; and one or more pharmaceutically acceptable carriers, excipients or diluents.

47. A method of treating asthma, inflammation, bronchitis, allergy, osteoporosis, dermatoses and disorders related to immune system, heart and kidney in a warm-blooded animal comprising administering a pharmaceutical composition that includes roflumilast prepared by the process of claim 43.

48. A compound of Formula II,

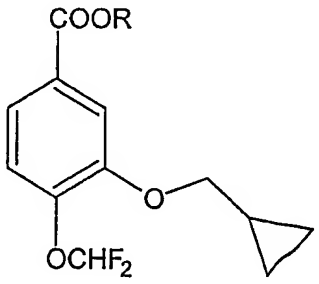


FORMULA II

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl.

49. The compound of claim 48, wherein R represents methyl or ethyl.

50. A compound of Formula III,



FORMULA III

wherein R represents alkyl of C_1-C_6, alkenyl of C_1-C_6, substituted or unsubstituted phenyl, benzhydryl, triphenylmethyl, or substituted or unsubstituted benzyl.

51. The compound of claim 50, wherein R represents methyl or ethyl.

INTERNATIONAL SEARCH REPORT

Int Application No
T/IB2004/002959

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C51/363 C07C51/347 C07C65/21 C07C67/00 C07C69/84
C07C69/92 A61K31/44 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/033430 A (ALBEMARLE CORPORATION) 22 April 2004 (2004-04-22) page 1, line 6 - line 12; example 3 page 6, line 15 - line 22	46,47, 50,51
X	REID P: "ROFLUMILAST" CURRENT OPINION IN INVESTIGATIONAL DRUGS, CURRENT DRUGS, LONDON, GB, vol. 3, no. 8, August 2002 (2002-08), pages 1165-1170, XP001119630 ISSN: 0967-8298 the whole document	46,47
A	US 5 712 298 A (AMSCHLER ET AL) 27 January 1998 (1998-01-27) cited in the application column 9 - column 11	1-51

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 February 2005	23/02/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Österle, C

INTERNATIONAL SEARCH REPORT

.....onal application No.
PCT/IB2004/002959

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 47 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern[illegible]pplication No
[illegible]IB2004/002959

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